Dangers related to the use of non-steroidal anti-inflammatory drugs

(Zagrożenia związane ze stosowaniem niesterydowych leków przeciw-zapalnych)

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Abstract – The paper discusses undesirable interactions of non-steroidal anti-inflammatory drugs (NSAIDs) with other drugs. Attention is paid to the toxicity of those medications. The particular focus is on the NSAIDs' impact on the gastrointestinal tract mucosa (especially in the stomach and duodenum).

Key words - non-steroidal anti-inflammatory drugs - NSAIDs, interaction, toxicity, damage to gastrointestinal tract mucosa.

Streszczenie – Autorzy omówili niepożądane interakcje niesterydowych leków przeciwzapalnych (NLPZ) w innymi lekami, zwrócili uwagę na toksyczne działanie tych specyfików. Dokładniej omówiono mechanizm działania NLPZ na błonę śluzową przewodu pokarmowego (zwłaszcza żołądka i dwunastnicy).

Słowa kluczowe - niesterydowe leki przeciwzapalne, interakcji, toksyczne działanie, uszkodzenia śluzówki przewodu pokarmowego.

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I. UNDESIRABLE OUTCOMES OF AN NSAID THERAPY

Undesirable outcomes of an NSAID therapy may pertain to patients of all ages. Nevertheless, the elderly are especially exposed to the undesirable effects of using NSAIDs. That is related to any possible disorders related to the absorption, distribution, metabolism and excretion of NSAIDs. The changes in renal and hepatic flow, the changed percentage of adipose tissue in the total body mass as well as different number and sensitivity of cell receptors may all be undesirably caused by the sustained NSAID treatment [1,2,3]. One has to remember that NSAIDs also may interact negatively with many other drugs, which makes the undesirable effects even more serious (Table 1).

Digoxin (Lanoxicaps, Lanoxin)
Oral anticoagulants
Phenytoin
Other non-steroidal anti-inflammatory drugs
Acetylsalicylic acid
Antihypertensive drug
Angiotensin converting enzyme inhibitors
Beta blockers
Diuretics
Methotrexate
Metoclopramide
Probenecid
Lithium salts

The undesirable effects of NSAIDs may pertain to varius systems and organs. Their toxicity may cause:

- Renal impairment resulting from taking NSAIDs; it is mostly not clinical and relieves soon after the patient stops taking the drug. However, acute renal failure sometimes occurs. The drugs in question may inhibit the prostaglandin synthesis, which causes white layer ischemia, which in turn provides the foundations for drug-induced nephropathy lesions. Patients who have a prior history of renal impairment or cardiac dysrhythmia, salt and water retention may become a clinical problem. The literature of the field also describes cases of interstitial nephritis and, more rarely, glomerulonephritis [1,4,6,7].

- Bronchospasm. Although it occurs rarely as a consequence of NSAID therapy, it is difficult to be prevented, especially if a patient is susceptible to a reaction of that kind. It seems that certain drugs, such as azapropazone and nabumetone, are free of such effects [1,4,5].

- Gristle and bone damage. The inhibition of the prostaglandin synthesis by strong NSAIDs has been believed to quickly cause damage to the head of femur ("indomethacin hip"). Currently, however, this mechanism is considered doubtful, as is the general thesis on gristle and bone damage caused by the drugs. While in vitro studies and tests on animals have shown that some NSAIDs do inhibit the synthesis of proteoglycans, others have been found to stimulate this synthesis, which however cannot justify the view endorsed by some authors that certain NSAIDs (e.g. azapropazone, diclofenac, sulindac) protect gristle [4,5,8,9].

- Certain NSAIDs (especially aspirin) may cause headaches and dizziness as well as tinnitus, which is related to the drug plasma concentration. Confusion and psychomotor function impairment also occur, mainly after indomethacin, which has the most serious consequences for the elderly. All undesirable consequences are dependent on the dose, although high tolerance and cross-tolerance are sometimes observed [4,7].

- The most common idiosyncratic effect of NSAIDs is a skin rash, even though its frequency is dependent on the particular drug. Usually, the most serious skin reactions occur after fenbufen [1,4,7].

- The use of NSAIDs is generally accompanied by insignificant and reversible increase in hepatic enzymes. However, cases of toxic hepatitis induced by aspirin, diclofenac, fenoprofen, naproxen have been described; and the use of sulindac may lead to reversible cholestatic jaundice [1,4,5].

- The most common and the most life-threatening undesirable effect of sustained NSAID treatment is related to the gastrointestinal tract [1,4,10,11,12]. For instance, the average risk of complications in gastrointestinal tract, rated in the rank system, is: 1.1 for ibuprofen, 2.9 for diclofenac, 5 for diflunisal, 3 for fenoprofen, 2.7 for salicylic acid, 4.4 for sulindac, 3.4 for naproxen, 4 for indomethacin, 5.1 for piroxicam, 4.7 for ketoprofen, 6.5 for tolmetin and 7.5 for azapropazone [5,6].
- Unfavourable effects of NSAIDs on gastrointestinal tract are most frequently reflected by dyspeptic symptoms such as nausea, flatulence, abdominal pain and defecation rhythm disorders. However, in some of the cases, dangerous damage to the mucosa of the gastrointestinal tract, duodenum and intestines occurs. The risk of drug-induced gastric ulceration pertains to 20-30% of patients treated with NSAIDs. With reference to duodenum ulceration, the percentage is 5-10%. These ulcerations often are clinically "mute", which often makes their complications (bleeding, perforation) the first symptoms of the disease [1,2,5,12].
- Nearly 70% of deaths resulting from the complications of gastric and duodenal ulcerations are the cases of NSAID-treated patients. The likelihood of dying of ulceration-related bleeding is four times as high in the elderly treated with NSAIDs as in those who do not take them [4,7].

II. THE MECHANISM OF THE DAMAGING IMPACT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON GASTRIC MUCOSA

The influence of NSAIDs on the mucosa of the upper gastrointestinal tract has been widely studied experimentally and clinically. It has been observed that gastric barrier is damaged by various complex mechanisms, regardless of where the drugs enter the organism [13,14,15]. The presumable mechanism of the mucosa damage caused salicylic acid is shown in figure 1.

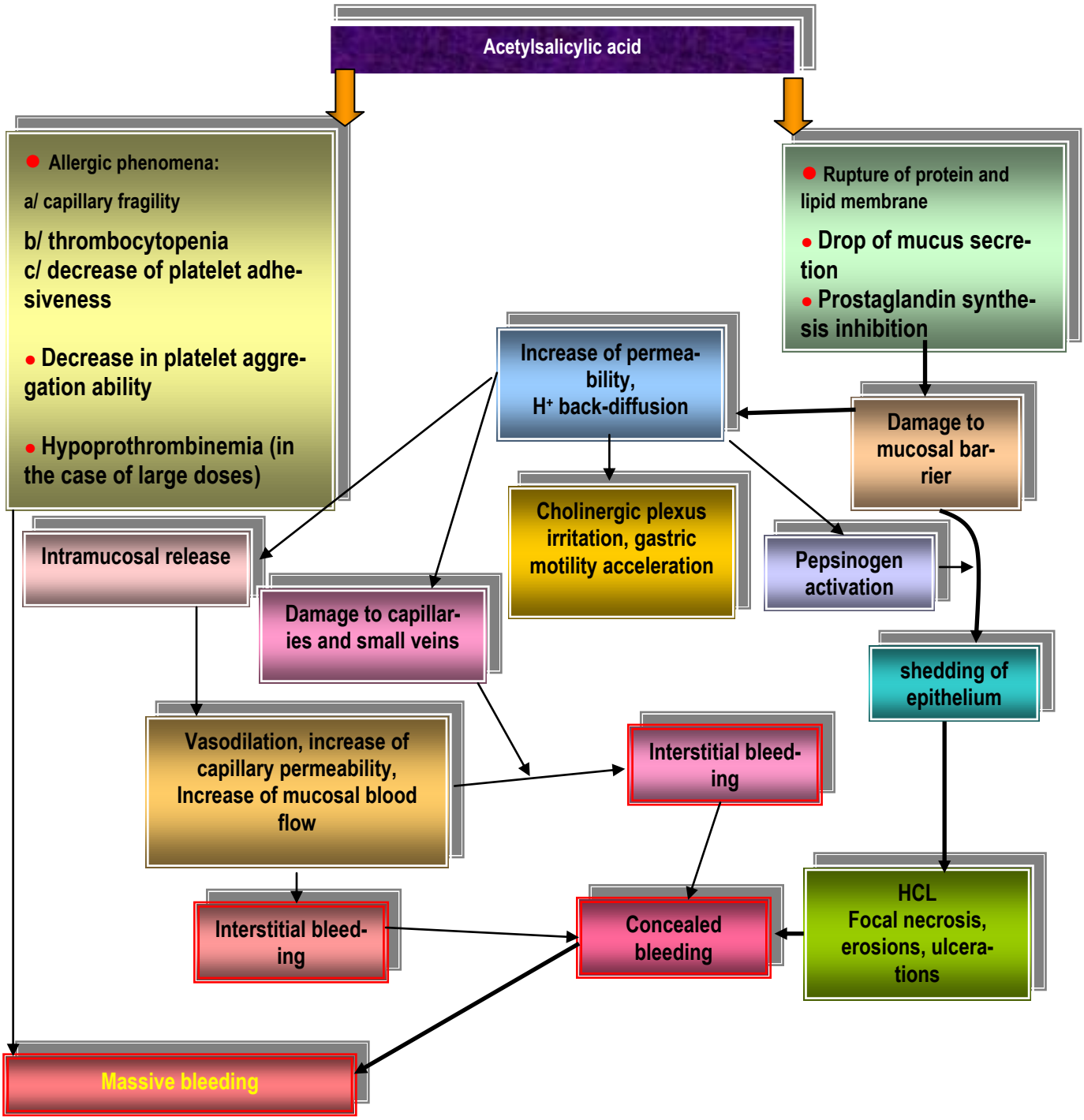

Figure1. The mechanism of the effect of acetylsalicylic acid on gastric mucosa [13,14,15]

Important as they are, local effects of NSAIDs do not seem pivotal with regard to the mucosal damage to upper gastrointestinal tract [11,13].

This is defended by the fact that such damage may be also inflicted by NSAIDs applied parenterally [15].

The main systemic mechanism of such damage may be associated with the NSAID effects consisting in the inhibition of prostaglandin synthesis in the stomach wall [11,14]. In physiological conditions, the protective effects of prostaglandins on mucosa are constituted by several mechanisms [14]:

- they protect the epithelial and glandular cells from the effects of cytotoxic factors
- they stimulate the release of bicarbonates
- they increase the mucus production and make it more resistant to the acid
- they inhibit the secretion of hydrochloric acid
- they protect the surface epithelium proliferation zone
- they sustain the functionality of microcirculation and the integration ability of vascular walls

In normal conditions, the cyclooxygenase 1 (COX-1) enzyme is employed in the production of prostaglandins in stomach walls. Many NSAIDs used nowadays are strong inhibitors of this enzyme.

Other mechanisms related to the harmful systemic effects of NSAIDs should be considered as well – for instance, a decrease in platelet aggregation (the inhibition of thromboxane A_2 synthesis in thrombocytes), which causes the deterioration of haemorrhagic lesions or the inhibition of the angiogenesis process. The clinical consequences of that might be the difficulty of ulceration healing in patients who use NSAIDs chronically [12,14].

III. REFERENCES

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